

20150

39



⑪ Publication number: **0 375 329 B1**

⑫ **EUROPEAN PATENT SPECIFICATION**

④⑤ Date of publication of patent specification: **31.05.95** ⑤① Int. Cl.⁸: **C07D 473/00, C07D 239/46, A61K 31/52, A61K 31/505**

②① Application number: **89313218.3**

②② Date of filing: **18.12.89**

The file contains technical information submitted after the application was filed and not included in this specification

⑤④ **Antiviral pyrimidine and purine compounds, process for their preparation and pharmaceutical compositions containing them.**

- ③① Priority: **19.12.88 GB 8829571**
07.03.89 GB 8905159
- ④③ Date of publication of application:
27.06.90 Bulletin 90/26
- ④⑤ Publication of the grant of the patent:
31.05.95 Bulletin 95/22
- ⑥④ Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE
- ⑤⑥ References cited:
EP-A- 0 072 027
EP-A- 0 099 493
EP-A- 0 308 065

JOURNAL OF MEDICINAL CHEMISTRY, vol. 26, no. 4, April 1983, pages 602-604, American Chemical Society, Columbus, Ohio, US; L COLLA et al.: "Synthesis and antiviral activity of water-soluble esters of acyclovir [9-[(2-hydroxyethoxy)methyl]guanine]"

- ⑦③ Proprietor: **THE WELLCOME FOUNDATION LIMITED**
Unicorn House
160 Euston Road
London NW1 2BP (GB)
- ⑦② Inventor: **Beauchamp, Lilla Marie**
3007 Wycliff Road
Raleigh, North Carolina 27607 (US)
- ⑦④ Representative: **Garrett, Michael et al**
The Wellcome Research Laboratories
Group Patents and Agreements
Langley Court
Beckenham
Kent BR3 3BS (GB)

EP 0 375 329 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

Description

The present invention relates to novel antiviral esters of pyrimidine and purine nucleosides containing an acyclic side chain.

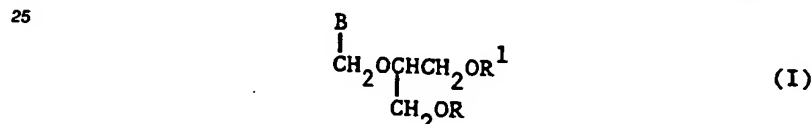
5 European Patent Specification 167385A describes and claims the antiviral pyrimidine nucleoside 1-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]cytosine and its physiologically acceptable salts and esters. The parent compound has been found to have particularly potent activity against cytomegalovirus (CMV) and Epstein-Barr virus (EBV).

The compound 9-[(2-hydroxy-1-hydroxymethylethoxy)methyl]guanine, which has the approved name 10 ganciclovir, is described in UK Patent Specification 2104070A which also describes generally the pharmaceutically acceptable salts and certain esters of ganciclovir. Ganciclovir has been found to have potent activity against viruses of the herpes family particularly herpes simplex and cytomegalovirus. Ganciclovir has however, low oral bioavailability and is typically administered as a 1-hour intravenous infusion every 12 hours.

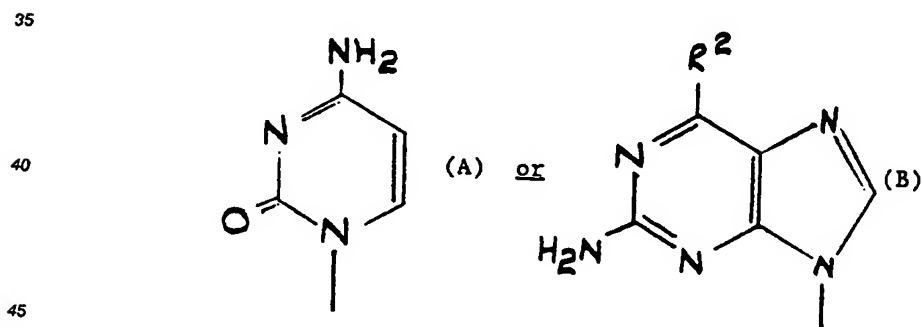
15 The 6-deoxy and 6-amino analogues of ganciclovir have also been described in the literature, the former being described in UK Patent Specification 2104070A and the latter in UK Patent Specification 2130204A.

We have now found that valine amino acid esters of the compounds referred to above surprisingly have advantageous bioavailability when administered by the oral route, resulting in exceptionally high levels of 20 the parent compound in the body. This enables less drug to be administered while still providing equivalent drug levels of the parent compound in the plasma. Oral administration means patient compliance is considerably simplified.

According to one feature of the present invention there is provided a compound of formula I:-



30 (wherein R and R¹ are independently selected from a hydrogen atom or a valine residue providing at least one of R and R¹ represents a valine residue and B represents a group of formula



in which R² represents a C₁₋₆ straight chain, C₃₋₆ branched chain or C₃₋₆ cyclic alkoxy group, or a hydroxy or an amino group) and the physiologically acceptable salts thereof.

A group falling within formula (I) above is where R² represents a hydroxy or an amino group. 50 It will be appreciated that the compound of formula (I) in which B represents a group of formula (B) wherein R² represents hydroxy is shown in the enol tautomeric form. The compound may also exist in its keto tautomeric form.

Among the above amino acid esters of formula (I) those of cytosine and ganciclovir are particularly preferred by virtue of their especially improved bioavailability in comparison with the parent compounds.

55 The valine amino acid esters according to the invention includes the mono- and di-esters of the compound of formula (I). The amino acids may be D-, L- and DL-amino acids, with the L-amino acids being most preferred.

Examples of preferred compounds of formula (I) above include those of Examples 1 and 2.

The above-mentioned physiologically acceptable salts are preferably acid addition salts derived from an appropriate acid, e.g., hydrochloric, sulphuric, phosphoric, maleic, fumaric, citric, tartaric, lactic or acetic acid.

The above-defined valine amino acid esters of formula (I) and their salts which are hereinafter referred to as the compounds according to the invention, are especially useful for the treatment or prophylaxis of virus infections, especially herpes infections such as herpes simplex, varicella zoster, Epstein-Barr virus (human herpes virus-6 infections), and particularly cytomegalovirus, in humans or non-human animals. Examples of clinical conditions which are caused by such viruses include herpetic keratitis, herpetic encephalitis, cold sores and genital infections (caused by herpes simplex), chicken pox and shingles (caused by varicella zoster) and CMV-pneumonia and -retinitis, particularly in immunocompromised patients including renal and bone marrow transplant patients and patients with Acquired Immune Deficiency Syndrome (AIDS). Epstein-Barr virus (EBV) causes infectious mononucleosis, and is also suggested as the causative agent of nasopharyngeal cancer, immunoblastic lymphoma, Burkitt's lymphoma and hairy leukoplakia.

According to further features of the present invention we provide :

- a) the compounds according to the invention for use in medical therapy particularly for the treatment or prophylaxis of viral infections, e.g., those referred to above;
- b) the use of the compounds according to the invention for the manufacture of a medicament for the treatment or prophylaxis of viral infections, e.g., those referred to above.

The compounds according to the invention may be administered for therapy by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, intraocular and epidural). It will be appreciated that the preferred route may vary with for example the condition of the recipient.

For each of the above-indicated utilities and indications the amount required of the compound according to the invention will depend upon a number of factors including the severity of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician. In general however, for each of these utilities and indications, a suitable, effective dose will be in the range 0.1 to 250mg per kilogram bodyweight of recipient per day, preferably in the range 1 to 100mg per kilogram bodyweight per day and most preferably in the range 5 to 20mg per kilogram bodyweight per day; an optimum dose is about 10mg per kilogram bodyweight per day. The desired dose is preferably presented as two, three, four or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1000mg, preferably 20 to 500mg and most preferably 100 to 400mg of the compound according to the invention per unit dosage form.

The compounds of the invention may be administered for the treatment or prophylaxis of viral infections alone or in combination with other therapeutic agents, for example, with other antiviral agents such as 9-(2-hydroxy-ethoxymethyl)guanine (acyclovir) used to treat herpes viral infections in particular HSV; with 3'-deoxy-3'-azidothymidine (zidovudine) or a 2',3'-dideoxynucleoside for example 2',3'-dideoxy cytidine, 2',3'-dideoxyinosine, 2',3'-dideoxyadenosine or 2',3'-dideoxyguanosine, used to treat retroviral infections in particular Human Immunodeficiency Virus (HIV) infections, interferons particularly α -interferon and soluble proteins such as CD4, or any other agents such as analgesics or antipyretics which when in combination with a compound of the invention provide a beneficial therapeutic effect.

While it is possible for the active ingredients to be administered alone it is preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the present invention comprise at least one compound according to the invention (also referred to hereafter as "the active ingredient"), together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, intraocular and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers of finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

For infections of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient in an amount of, for example, 0.075 to 20% w/w, preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulphoxide and related analogues.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerine, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Formulations for intramuscular administration are particularly preferred.

Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The present invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

5 For oral administration the compositions can be in the form of a tablet, granule, drench, paste, cachet, capsule or feed supplement. Granules may be made by the well known techniques of wet granulation, precompression or slugging. They can be administered to animals in an inert liquid vehicle so as to form a drench, or in a suspension with water or oil base. Preferably further accessory ingredients such as a dispersing agent are included. These formulations preferably contain from 15 to 85% of the active
10 ingredient.

The compounds according to the invention may be prepared in conventional manner, e.g. by a process as described below.

Thus, according to a further feature of the present invention we provide a process for the preparation of the compounds according to the invention which comprises reacting the compound of formula (II)

15



20

(wherein B is as hereinbefore defined) with an optionally protected valine amino acid or functional equivalent thereof and optionally effecting one or more of the following conversions:-

- 25 i) removal of any protecting groups;
ii) where the resulting product is a compound of formula (I), conversion of the said compound into a physiologically acceptable salt thereof; and
iii) where the resulting product is a physiologically acceptable salt of a compound of formula (I),
30 conversion of the said salt into the parent compound.

30 In the above process, the reaction may be carried out in a conventional manner, for example in a solvent such as pyridine, dimethylformamide etc., in the presence of a coupling agent such as N,N - dicyclohexylcarbodiimide, optionally in the presence of a catalytic base such as 4-dimethylaminopyridine. The water formed during the reaction may, if desired, be removed in conventional manner, for example by distillation or by the addition of a water-binding substance. Subsequently, the ester obtained as reaction
35 product may be isolated in conventional manner.

As an alternative to the use of the valine amino acid per se, a functional equivalent of the acid may be employed, e.g., an acid halide such as the acid chloride, or an acid anhydride.

In order to avoid undesirable side-reactions, it may be advantageous to use an amino-protected derivative, examples of preferred amino-protecting groups including acyl, e.g., C₁₋₄ alkanoyl such as acetyl; 40 arylalkyloxycarbonyl, e.g., benzyloxycarbonyl; or aminoprecursor groups such as azido groups. It is particularly preferred to employ an amino acid protected by a benzyloxycarbonyl group. Such benzyloxycarbonyl protected compounds are commercially available, e.g., from Sigma Chemical Co., USA, or may be prepared by treating the appropriate amino acid with carbobenzoxy chloride in alkaline solution.

The optional conversions i), ii) and iii) may be effected in a conventional manner. Thus, for example, 45 removal of protecting groups in conversion i) may be effected by hydrogenolysis or as appropriate. With regard to removal of protecting groups on the amino acid acyl radicals, hydrogenolysis, e.g., of arylalkyloxycarbonyl protecting groups, and conversion of azido group, e.g., by catalytic hydrogenation, e.g., using a palladium catalyst, are preferred.

The conversion of an amino acid ester into a physiologically acceptable salt may be effected in 50 conventional manner, e.g., by treatment of the compound with an appropriate acid to form an acid addition salt.

Similarly, conversion of a salt into the parent amino acid ester may be effected in conventional manner for example, by treatment with a stoichiometric amount of an ion exchange resin (basic form), filtration to remove the resin and lyophilisation of the resulting solution.

55 The following Examples illustrate the present invention.

Example 1

a) 2-((4-((N-((benzyloxy)carbonyl)-L-valinamido)-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy)-1,3-propanediyl bis(N-((benzyloxy)carbonyl)-L-valinate) and 2-((4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy)-1,3-propanediyl bis(N-((benzyloxy)carbonyl)-L-valinate)

A suspension of 2 g of 4-amino-1-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-2(1H)-pyrimidinone in 40 mL dry dimethylformamide (DMF) was slightly warmed until a clear solution remained. 5.84g of CBz-L-valine, 567 mg of dimethylaminopyridine (DMAP) and 4.79 g of dicyclohexylcarbodiimide (DCC) was successively added. A white precipitate was observed after 15 min. The mixture was stirred at room temperature for 4 h. The resulting suspension was filtered and the filtrate distributed between water and CH₂Cl₂. The organic fraction was dried (MgSO₄), filtered and evaporated in vacuo to a yellow oil. The oil was purified by flash chromatography of silica gel. Eluting with 2% methanol in dichloromethane afforded the triacylated derivative, 1.12 g (13%) as a white foam.

Eluting with 4% methanol in dichloromethane afforded the N,O,O-triacylated derivative, 113 mg (2%).

Eluting with 10% methanol in dichloromethane afforded the O,O-diacylated derivative, 3.44 g (54%) as a white foam.

b) 2-((4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy)-1,3-propanediyl bis(L-valinate)

To a cool mixture of 3.44 g of 2-((4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy)-1,3-propanediyl bis(N-((benzyloxy)carbonyl)-L-valinate) and 7g of 10% palladium catalyst in acetic acid was slowly added 8.65 mL of 1,4-cyclohexadiene. The mixture was allowed to stir at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite. The filtrate was then concentrated and dried in the lyophilizer for 48 h. The resulting beige foam was scraped off affording 2.38 g (68%, as the acetic acid salt) of the title compound. The elemental analysis (showing 2M of acetic acid and 1M of water) UV, ¹H, ¹³C-NMR spectra were consistent with the title structure.

Example 2

2-((2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(L-valinate)

a) 2-((2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(N-((benzyloxy)carbonyl)-L-valinate)

A solution of 22.5g(0.09M) of N-benzyloxycarbonyl chloride (Sigma Chemical Co.) Lvaline, 18.6g (0.09mol) of N,N-dicyclohexylcarbodiimide and 1.2g (0.01mol) of 4-dimethylaminopyridine in 100mL of dimethylformamide was stirred under nitrogen for 10 minutes. After the addition of 20mL more of dimethylformamide and 7.65g (0.03mol) of 9-(1,3-dihydroxypropoxymethyl)guanine, the mixture was stirred for 18 hours at ambient temperature.

The suspension was filtered, washing the precipitate with dichloromethane and the combined filtrate and washings were evaporated in vacuo. The residual yellow oil was dissolved in methanol and absorbed on silica gel. The mixture was evaporated in vacuo and the powdery residue added to a column prepared for flash chromatography. The column was eluted first with 2% methanol in dichloromethane to remove an impurity and the desired product was then eluted off with 5% methanol in dichloromethane. Evaporation of this eluate gave 14.3g (66%) of 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis (N-((benzyloxy)carbonyl)-L-valinate), which gave a satisfactory elemental analysis, ¹H NMR and ¹³C spectra.

b) 2-((2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(L-valinate)

A mixture of 0.722g (1.0mmol) of 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(N-((benzyloxy)carbonyl)-L-valinate) and 300mg of 10% palladium on carbon in 10mL of acetic acid was shaken in a Parr apparatus at ambient temperature at an initial pressure of 50 psi for 18 hours. The mixture was filtered through a pad of celite, washing the pad with acetic acid. The filtrate was evaporated at room temperature under pump vacuum giving a syrup (822mg) which was dried at 100 °C with 1.0mm pressure. The resulting glass turned to a solid on scraping with a spatula and was the desired 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(L-valinate). The compound gave satisfactory ¹H NMR, ¹³C, UV and Mass spectra. It analyzed for 2 moles of acetic acid and 0.05 moles of water.

The following Examples, 3 to 5, illustrate pharmaceutical formulations according to the invention where the active ingredient is a compound according to the invention.

Example 3Tablet

5

10

Active compound	200mg
Lactose	235mg
Starch	50mg
Polyvinylpyrrolidone	50mg
Magnesium stearate	5mg

Mix the active compound with the lactose and starch and wet granulate with a solution of the polyvinylpyrrolidone. Dry, sift, blend the granules with magnesium stearate and compress.

15

Example 4Capsule

20

25

Active compound	200mg
Lactose	184mg
Sodium starch glycollate	8mg
Polyvinylpyrrolidone	6mg
Magnesium stearate	2mg

Mix the active compound with the lactose and sodium starch glycollate and wet granulate with a solution of the polyvinylpyrrolidone. Dry, sift, blend the granules with the magnesium stearate and fill into hard gelatin capsules.

30

Example 5Intravenous Injections

35

40

A)	Active compound	200mg
	Sodium hydroxide solution	q.s. to pH 7.0 to 7.5
	Water for injections to	5.0ml

Dissolve the active compound in part of the water for injections. Adjust the pH with the sodium hydroxide solution and make up to volume with additional water for injections. Under aseptic conditions, sterilise the solution by filtration, fill into sterile ampoules and seal the ampoules.

45

50

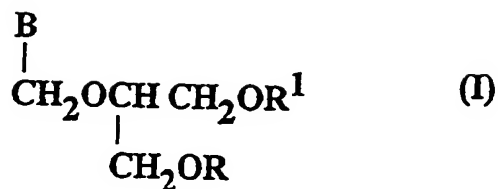
B)	Active compound	100mg
	Sodium hydroxide solution	q.s. to pH 7.0 to 7.5
	Mannitol	125mg
	Water for injections to	2.5ml

Dissolve the active compound and mannitol in part of the water for injections. Adjust the pH with the sodium hydroxide solution and make up to volume with additional water for injections. Under aseptic conditions, sterilise the solution by filtration, fill into sterile vials and remove the water by freeze-drying. Seal the vials under an atmosphere of nitrogen and close with a sterile stopper and aluminium collar.

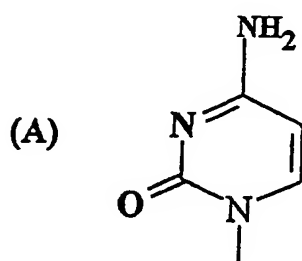
55

Claims

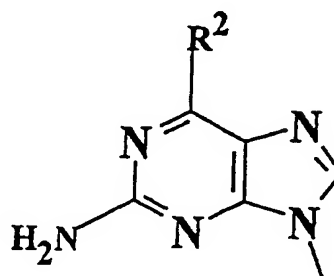
1. A compound of formula (I):



(wherein R and R¹ are independently selected from a hydrogen atom or a valine residue providing at least one of R and R¹ represents a valine residue and B represents a group of formula

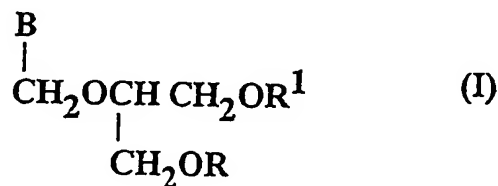


or (B)

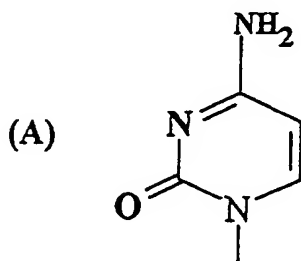


in which R² represents a C₁₋₆ straight chain, C₃₋₆ branched chain or C₃₋₆ cyclic alkoxy group or a hydroxy or an amino group) and physiologically acceptable salts thereof.

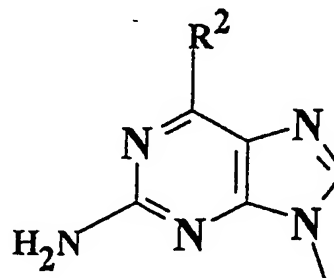
2. A compound of formula (I):



(wherein R and R¹ are independently selected from a hydrogen atom or a valine residue providing at least one of R and R¹ represents a valine residue and B represents a group of formula

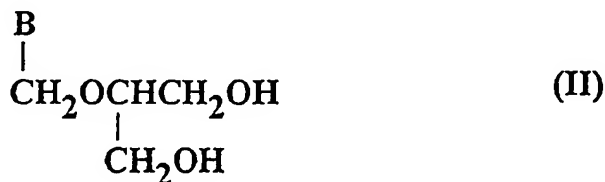


or (B)



in which R² represents a hydroxy or an amino group and physiologically acceptable salts thereof.

3. A compound of formula (I) 2-((4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)methoxy)-1,3-propanediyl bis (L-valinate).
4. A compound of formula (I) 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis (L-valinate).
5. A compound of formula (I) as claimed in claims 1 or 2 in which all valine groups are in the L-form.
6. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 and physiologically acceptable salts thereof for use in medical therapy.
7. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 and physiologically acceptable salts thereof for use in the treatment or prophylaxis of viral infections.
8. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 and physiologically acceptable salts thereof for use in the treatment or prophylaxis of herpes virus infections.
9. A compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 and physiologically acceptable salts thereof for use in the treatment or prophylaxis of a cytomegalovirus infection.
10. Use of a compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 and physiologically acceptable salts thereof in the manufacture of a medicament for the treatment or prophylaxis of viral infections.
11. A pharmaceutical formulation comprising as active ingredient a compound of formula (I) as claimed in claim 1, 2, 3, 4 or 5 or a physiologically acceptable salt thereof together with at least one pharmaceutically acceptable carrier therefor.
12. A pharmaceutical formulation as claimed in claim 11 adapted for oral or parenteral administration.
13. A pharmaceutical formulation as claimed in claim 11 in the form of a tablet or capsule.
14. A process for the preparation of a compound of formula (I) (as defined in claim 1) and physiologically acceptable salts thereof which comprises reacting a compound of formula (II)

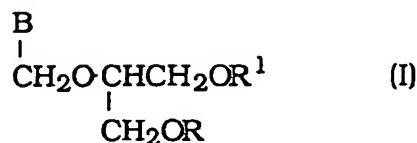


(wherein B is as defined in claim 1) with an optionally protected valine or a functional equivalent thereof and optionally effecting one or more of the following conversions:

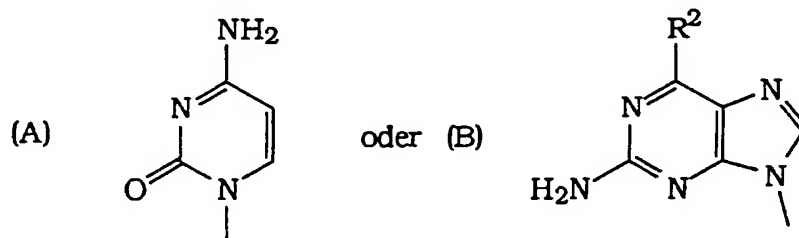
- i) removal of any protecting groups;
- ii) where the resulting product is a compound of formula (I), conversion of the said compound into a physiologically acceptable salt thereof; and
- iii) where the resulting product is a physiologically acceptable salt of a compound of formula (I), conversion of the said salt into the parent compound.

Patentansprüche

1. Verbindung der Formel (I):

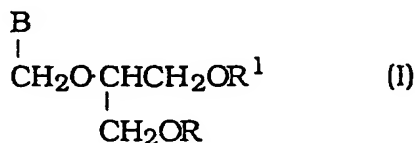


(worin R und R¹ unabhängig voneinander aus Wasserstoffatomen und Valin-Resten ausgewählt sind, mit der Maßgabe, daß mindestens einer der Reste R und R¹ einen Valin-Rest darstellt, und B eine Gruppe der Formel

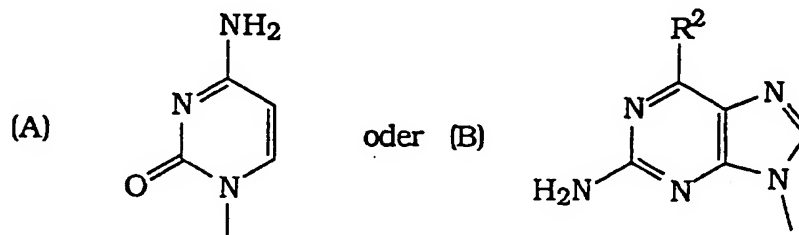


bedeuten, worin R² eine geradkettige C₁₋₆-Alkoxygruppe, verzweigt-kettige C₃₋₆-Alkoxygruppe, eine cyclische C₃₋₆-Alkoxygruppe, eine Hydroxylgruppe oder eine Aminogruppe darstellt) und deren physiologisch annehmbare Salze.

2. Verbindung der Formel (I):

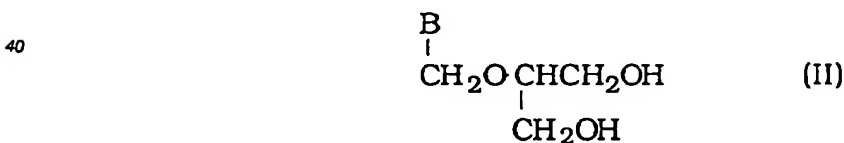


(worin R und R¹ unabhängig voneinander aus Wasserstoffatomen und Valin-Resten ausgewählt sind, mit der Maßgabe, daß mindestens einer der Reste R und R¹ einen Valin-Rest darstellt, und B eine Gruppe der Formel



bedeuten, worin R² eine Hydroxylgruppe oder eine Aminogruppe darstellt) und deren physiologisch annehmbare Salze.

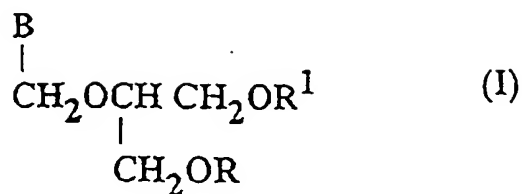
3. Verbindung der Formel (I), nämlich 2-((4-Amino-1,2-dihydro-2-oxo-1-pyrimidinyl)-methoxy)-1,3-propan-
diyl-bis(L-valinat).
- 5 4. Verbindung der Formel (I), nämlich 2-((2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)-methoxy)-1,3-propan-
diyl-bis(L-valinat).
5. Verbindung der Formel (I) nach den Ansprüchen 1 oder 2, worin sämtliche Valin-Gruppen in der L-
Form vorliegen.
- 10 6. Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 und deren physiologisch annehmbare
Salze zur Verwendung in der medizinischen Therapie.
7. Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 und deren physiologisch annehmbare
Salze zur Behandlung oder Prophylaxe von Virusinfektionen.
- 15 8. Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 und deren physiologisch annehmbare
Salze zur Verwendung bei der Behandlung oder Prophylaxe von Herpes-Virusinfektionen.
9. Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 und deren physiologisch annehmbare
20 Salze zur Verwendung bei der Behandlung oder Prophylaxe einer Cytomegalovirus-Infektion.
10. Verwendung einer Verbindung der Formel (I) nach den Ansprüchen 1, 2, 3, 4 oder 5 und der
physiologisch annehmbaren Salze davon bei der Herstellung eines Arzneimittels zur Behandlung oder
Prophylaxe von Virusinfektionen.
- 25 11. Pharmazeutische Zubereitung enthaltend als Wirkstoff eine Verbindung der Formel (I) nach den
Ansprüchen 1, 2, 3, 4 oder 5 oder ein physiologisch annehmbares Salz davon zusammen mit
mindestens einem dafür geeigneten pharmazeutisch annehmbaren Trägermaterial.
- 30 12. Pharmazeutische Zubereitung nach Anspruch 11, die für die orale oder parenterale Verabreichung
geeignet ist.
13. Pharmazeutische Zubereitung nach Anspruch 11, die in Form einer Tablette oder einer Kapsel vorliegt.
- 35 14. Verfahren zur Herstellung einer Verbindung der Formel (I) (wie sie in Anspruch 1 definiert ist) und von
deren physiologisch annehmbaren Salzen, welches darin besteht, eine Verbindung der Formel (II)



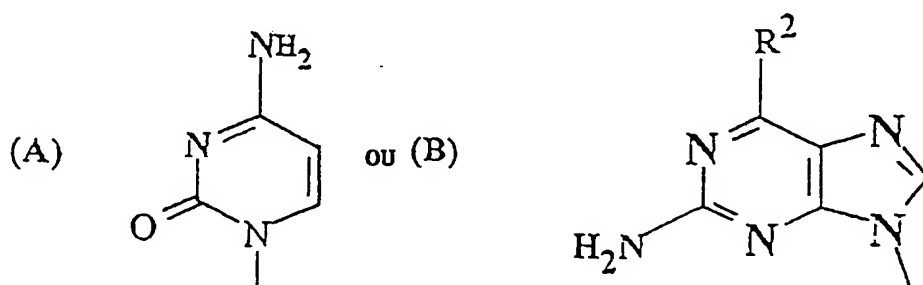
- 45 (worin B die in Anspruch 1 angegebenen Bedeutungen besitzt) mit einem gegebenenfalls geschützten
Valin oder einem funktionellen Äquivalent davon umzusetzen und gegebenenfalls eine oder mehrere
der folgenden Umwandlungen zu bewirken:
- i) Abspaltung von eventuell vorhandenen Schutzgruppen;
 - 50 ii) Umwandlung einer Verbindung der Formel (I) in ein physiologisch annehmbares Salz davon; und
 - iii) Umwandlung eines physiologisch annehmbaren Salzes einer Verbindung der Formel (I) in die
Mutterverbindung.

Revendications

1. Composé de formule (I) :

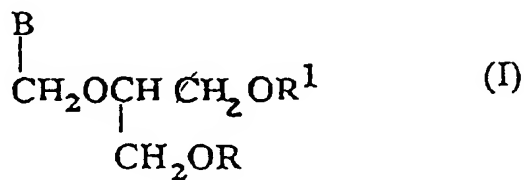


(dans laquelle R et R¹ sont choisis indépendamment parmi un atome d'hydrogène ou un résidu valine, à condition qu'au moins un des groupes R et R¹ représente un résidu valine et B représente un groupe de formule

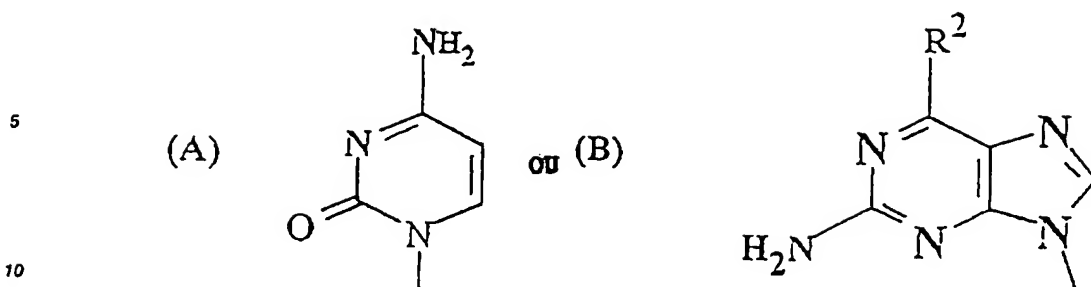


dans laquelle R² représente une chaîne droite en C₁₋₆, une chaîne ramifiée en C₃₋₆ ou un groupe alkoxy cyclique en C₃₋₆ ou un groupe hydroxy ou un groupe amino) et des sels physiologiquement acceptables de ceux-ci.

2. Composé de formule (I) :

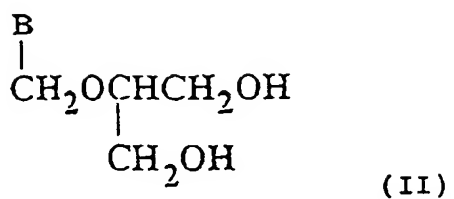


(dans laquelle R et R¹ sont choisis indépendamment parmi un atome d'hydrogène ou un résidu valine à condition qu'au moins un des groupes R et R¹ représente un résidu valine et B représente un groupe de formule



dans laquelle R² représente un groupe hydroxy ou un groupe amino et des sels physiologiquement acceptables de ceux-ci.

- 15
3. Composé de formule (I) 2-((4-amino-1,2-dihydro-2-oxo-1-pyrimidinyl)méthoxy)-1,3-propanediyl bis (L-valinate).
4. Composé de formule (I) 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)méthoxy)-1,3-propanediyl bis (L-valinate).
- 20
5. Composé de formule (I) tel que revendiqué dans les revendications 1 ou 2 dans lequel tous les groupes valine sont sous la forme L.
6. Composé de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 et des sels physiologiquement acceptables de celui-ci pour usage dans une thérapie médicale.
7. Composé de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 et des sels physiologiquement acceptables de celui-ci pour usage dans le traitement curatif ou préventif d'infections virales.
- 30
8. Composé de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 et des sels physiologiquement acceptables de celui-ci pour usage dans le traitement curatif ou préventif d'infections par le virus de l'herpès.
9. Composé de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 et des sels physiologiquement acceptables de celui-ci pour usage dans le traitement curatif ou préventif d'une infection par le cytomégalovirus.
- 35
10. Utilisation d'un composé de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 et des sels physiologiquement acceptables de celui-ci dans la préparation d'un médicament pour le traitement curatif ou préventif d'infections virales.
- 40
11. Formulation pharmaceutique comprenant comme ingrédient actif un composé de formule (I) tel que revendiqué à la revendication 1, 2, 3, 4 ou 5 ou des sels physiologiquement acceptables de celui-ci avec au moins un véhicule pharmaceutiquement acceptable pour celui-ci.
- 45
12. Formulation pharmaceutique telle que revendiquée à la revendication 11 adaptée à une administration par voie orale ou parentérale.
13. Formulation pharmaceutique telle que revendiquée à la revendication 11 sous la forme d'un comprimé ou d'une capsule.
- 50
14. Procédé pour la préparation d'un composé de formule (I) (tel que défini à la revendication 1) et des sels physiologiquement acceptables de celui-ci qui comprend une étape consistant à faire réagir un composé de formule (II)
- 55



(dans laquelle B est tel que défini à la revendication 1) avec un groupe valine éventuellement protégé ou un équivalent fonctionnel de celui-ci et, éventuellement une étape consistant à effectuer une ou plusieurs des conversions suivantes :

- i) élimination de tous les groupes de protection ;
- ii) lorsque le produit résultant est un composé de formule (I), conversion dudit composé en un sel physiologiquement acceptable de celui-ci ; et
- iii) lorsque le produit résultant est un sel physiologiquement acceptable d'un composé de formule (I), conversion dudit sel en le composé de formule (I)